PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PN/4-33177A	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/005042	International filing date *(day/month/year)* 11.05.2004	Priority date *(day/month/year)* 12.05.2003

International Patent Classification (IPC) or national classification and IPC
C07D471/08, A61K31/4725, A61P25/28

Applicant
NOVARTIS AG et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04.12.2004	29.06.2005

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer
Telephone No. +49 89 2399- 8937

Wellstood

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/005042

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-10 as originally filed

   Claims, Numbers

   1-8 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☒ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 8

because:

☒ the said international application, or the said claims Nos. 8 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-8
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Re Item I

Basis of the opinion

The application is directed to

(i) N-azabicyclyl isoquinoline-3-carboxamides (I) (claim 1),
(ii) a process for preparing compounds (I) (claim 2),
(iii) the medical use of compounds (I) (claims 3-4 and 6-7),
(iv) the corresponding pharmaceutical composition (claim 5), and
(v) a method of treatment (claim 8).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 8 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents.

D1: WO 02/085901 A, 31 October 2002.
D2: WO 03/037896 A , 8 May 2003.
D3: WO 03/022856 A, 20 March 2003.
D4: WO 03/072578 A, 4 September 2003.
D5: WO 2004/052461 A, 24 June 2004.
D6: WO 2004/052348 A, 24 June 2004.

D4 to **D6** were published after the priority date. Under the presumption that the priority is valid for the claimed matter these documents are not considered as prior art under Rule 64.1 PCT.

2. Novelty

2.1 **D1** to **D3** relate to N-azabicyclyl carboxamides as α7 nAChR agonists. The present compounds (I) differ from the compounds of **D1** and **D2** through their isoquinoline moiety, and from the compounds of D3 insofar as their azabicyclyl moiety is represented by 1-azabicyclo[2.2.2]octane and 1-azabicyclo[2.2.1]-heptane rather than 7-azabicyclo[2.2.1]-heptane. The present claimed matter is thus novel vis-à-vis **D1** to **D3**.

2.2 **D4** to **D6** relate to further α7 nAChR agonists, their preparation, and pharmaceutical use. The compounds of these documents comprise already the present compounds (I) (D4, claim 1; D5, claims 1 and 3; D6, claim 1), and the documents disclose specific examples within the overlapping range (D4: examples 13, 14; page 120, claim 8; page 123, claim 9; page 125, claim 11; pages 127-128, claim 12, etc.; D5: claim 4; D6: claim 3). In the regional phase, these documents will most likely become relevant to the question of novelty of present claims 1-8 insofar as the whole overlapping range is concerned.

3 Inventive Step

3.1 The application describes the synthesis of certain compounds (I) which according to the description act as α7 nAChR agonists (page 3) and are expected to be useful in the treatment of psychotic disorders, neurodegenerative disorders, and further pathological conditions.

3.2 **D3** is at present considered as most relevant state of the art, because it shows already a N-azabicyclyl isoquinoline-3-carboxamide (example 9) of the desired activity. The present compounds (I) differ from the compounds of D3 merely insofar as their azabicyclyl moiety is represented by 1-azabicyclo[2.2.2]octane and 1-azabicyclo[2.2.1]heptane rather than 7-azabicyclo[2.2.1]-heptane. In view of **D3** the problem underlying the present application may be seen in the provision of further compounds which act as α7 nAChR agonists. The documents **D1** and **D2** disclose further α7 nAChR agonists and show that 1-azabicyclo[2.2.2]octane and 1-azabicyclo[2.2.1]heptane moieties are compatible with the desired activity (cf. D1, claim 1, examples 1a, 2a, 2b; D2, claim 1, and e.g. examples 1-3). Due to the very close structural relationship between the claimed compounds and the compounds of **D3** in combination with the teaching of **D1** and/or **D2**, the claimed compounds would appear to represent merely obvious alternatives of the compounds of **D3**. In the absence of any substantiated unexpected effect(s) of the

claimed compounds in comparison with the closest related compound of **D3** (i.e. N-[(1S,2R,4R)-1-azabicyclo[2.2.1]hept-2-yl]isoquinoline-3-carboxamide dihydrochloride versus example 9 of D3), no inventive activity is seen in the claimed matter. Hence, the claims 1-8 do, at present, not meet the requirements of inventive step.

4 Industrial Applicability

For the assessment of present claim 8 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 03/072578	04.09.2003	14.02.2003	20.02.2002
WO 2004/052461	24.06.2004	28.11.2003	11.12.2002
WO 2004/052348	24.06.2004	28.11.2003	11.12.2002

Re Item VII

Certain defects of the international application

The relevant background art disclosed in **D1** to **D3** is not mentioned in the description, nor are these documents identified therein (Rule 5.1(a)(ii) PCT).